PRECLINICAL DRUG
DEVELOPMENT TESTING FOR

药明康德
WuXi AppTec

RESPIRATORY MEDICATIONS

Shorten the Development Cycle with WuXi AppTec DMPK

Therapeutic Areas Series

Unique Pharmacokinetics Evaluation System for Respiratory Medications

Developing inhaled medications comes with unique pharmacokinetic challenges compared to traditional oral and injectable drugs. At WuXi AppTec DMPK, we specialize in overcoming these complexities with cutting-edge technology, advanced equipment, and deep expertise in inhaled drug research. Our comprehensive preclinical services support every stage of development, including intranasal administration, intratracheal administration, and nose-only inhalation exposure—helping you bring innovative respiratory therapies to market with confidence.

Since 2013, WuXi AppTec DMPK has focused extensively on respiratory medications, building substantial R&D experience. In addition to conventional administration routes, we have mastered the complexities of inhaled drug delivery—supporting over 100 inhaled drug projects and advancing numerous respiratory therapies to the clinical stage.

Strengths

- 10+ years of experience in respiratory medication
- Multiple routes of drug administration
- Integrated drug R&D services

Features

- Rigorous formulation properties
- Meticulous experimental operation
- Regulatory guidance

WuXi AppTec DMPK Study Strategy

▶Preclinical DMPK studies for respiratory medications

For systemically administered respiratory drugs, the study strategy builds on conventional systemic drug research including *in vitro* ADME, drug-drug interaction, and *in vivo* PK studies, with a particular focus on how test articles distribute within lung tissue.

For inhaled respiratory drugs, which can also enter the system through transpulmonary absorption or ingestion, the development approach is aligned with systemic drug development strategies and includes stability testing in the lungs. In early stage development, physicochemical property studies are recommended to support formulation screening.

Assay type		Discovery		IND filing	
		Systemic admin.	Inhalation admin.	Systemic admin.	Inhalation admin.
In vitro	Caco-2 cell permeability	✓		✓	Optional
	In vitro plasma protein binding	✓	✓	✓	✓
	Metabolic stability (liver microsomes and hepatocytes)	✓	✓	✓	✓
	Metabolic stability (lung microsomes/ lung S9/lung homogenate)				Optional
	Metabolite identification (liver microsomes and hepatocytes)	✓	✓	✓	✓
	Metabolizing enzyme phenotyping			✓	✓
	Drug-drug interaction	✓	✓	✓	✓
	Physicochemical properties	✓	✓		
In vivo	Bioavailability	✓	✓ (With oral bioavailability studies)	✓	✓
	Plasma PK of Intravenous and extravascular administration in rodents and non-rodents	✓	✓	✓	✓
	Tissue distribution (with special attention to lung)	✓	✓	✓	✓
	Drug concentration in bronchoalveolar lavage fluid (concentration in lung epithelial lining fluid)		Optional		Optional
	Biliary, fecal, and urinary excretion			✓	✓
	In vivo metabolite identification			✓	✓
	QWBA (quantitative whole-body autoradiography)			Optional	Optional

WuXi AppTec DMPK Study Strategy

▶Selection of the delivery devices

Drug development phase >	Preclinical discovery >	Preclinical development >	IND filing
Device	Intratracheal/Intranasal administration	Nose-only inhalation/intratracheal/ intranasal administration	Nose-only inhalation/intratracheal/ intranasal administration
Compound amount	Milligram	Gram	Gram
Compound property	Undetermined particle size and properties	Preliminary characterization	Determined properties and particle size

▶*In vivo* PK study strategy for nose-only exposure inhalation administration

The PK study of drugs delivered via nose-only exposure inhalation consists of two parts: validation of the drug delivery system and animal studies. In the validation study, the final study conditions—such as nebulization efficiency, humidity, formulation concentration—and port concentration are determined by evaluating the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the aerosol and optimizing the aerosol properties (Figure 3).

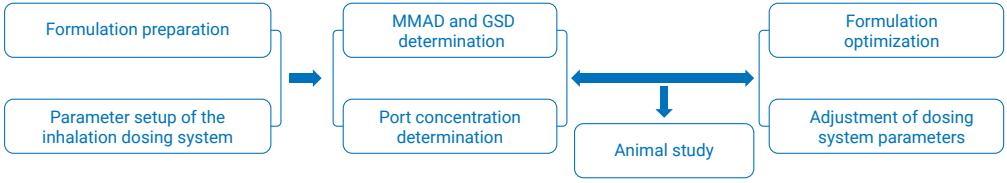
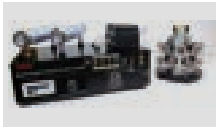


Figure 3. *In vivo* PK study strategy for nose-only inhalation administration

WuXi AppTec DMPK Respiratory Medication Platform

▶Device for inhalation administration

Nose-only exposure inhalation administration



Nose-only exposure inhalation tower

Ultrasonic nebulizer

Dry powder generator

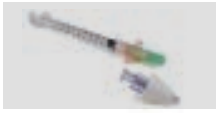
Photometers

Filter

Cascade

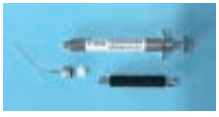
Intranasal administration

Intranasal instillation



Intranasal nebulizer

Intratracheal nebulization administration



Nebulization syringe

DPI-specific syringe

WuXi AppTec DMPK Respiratory Medication Platform

▶Physicochemical property testing and vehicle screening

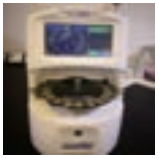
Physicochemical properties are crucial for early-stage formulation screening. WuXi AppTec DMPK has built a robust platform for physicochemical property testing and has extensive experience in formulation screening.

NEPHELOstar® Plus Nephelometer

SiriusT3

Covaris® E200x Ultrasonic Dispersers

Malvern® Mastersizer 3000 Laser Diffraction



Osmolality Pro

▶Bioanalysis

WuXi AppTec DMPK has extensive experience in biological sample analysis leveraging high-precision analytical instruments to achieve sensitive bioanalysis across various sample types. Our well-established ligand-binding assay and liquid chromatography-mass spectrometry (LC-MS/MS) analysis platforms enable the quantification of large and small molecule drugs in samples. The platform can simultaneously detect urea concentration (as a correction factor) in plasma/serum and bronchoalveolar lavage fluid (BALF) samples. The analysis of respiratory medications, such as inhaled monoclonal antibodies, is arduous and requires high sensitivity. The detection limit of the enzyme-linked immunosorbent assay/Meso Scale Discovery (MSD) method that we developed is as low as 1 ng/mL. We are also equipped with LC-MS/MS and MSD devices for the detection of biomarkers related to lung diseases, including lysophosphatidic acid (LPA16:0, 18:0, 18:1, 18:2, 20:4) and cytokines.

SCIEX 6500+ Quad™ 6500

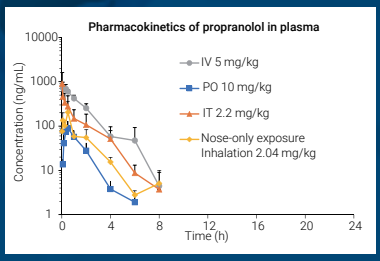
SpectraMax M5/M5e

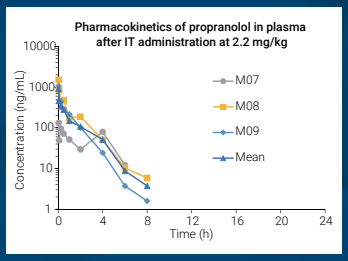
Case Study

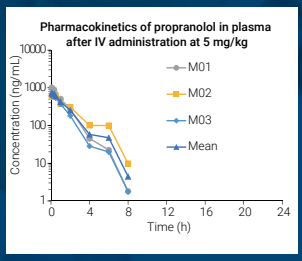
Using propranolol, a small-molecule drug, as an example, researchers investigated the bioavailability of three delivery methods: conventional oral administration (PO), intratracheal nebulization (IT), and nose-only inhalation exposure.

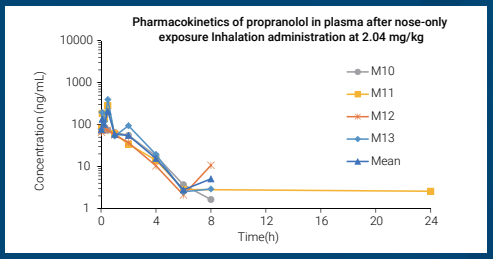
Experimental design: 13 mice were randomly divided into four groups and given propranolol via intravenous injection, PO, IT, and nose-only exposure inhalation. After dosing, plasma samples were collected to measure the drug concentrations.

The pharmacokinetic curves for each dose route are shown below, and the PK parameters are shown in the table. Due to the extensive hepatic first-pass effect, the bioavailability of propranolol of oral administration was low. However, the bioavailability increased significantly after IT and nose-only exposure inhalation. The results of this study provided data to support altering the administration route, reducing the treatment dosage, and improving the bioavailability of drugs with low oral bioavailability, especially for pulmonary diseases.









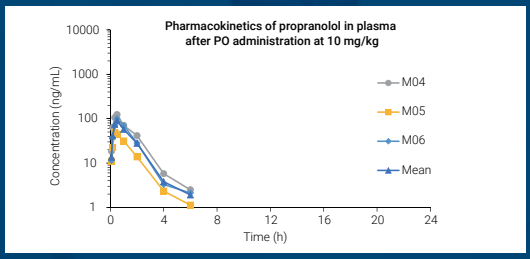


Table 1. System exposure after propranolol hydrochloride administration via different routes

Dose route	Dose level (mg/kg)	C_0/C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng.h/mL)	Bioavailability
IV	5	832	1341	-
PO	10	90.7	135	5.05%
IT	2.2	907	633	107%
Nose-only exposure inhalation	2.04	210	286	52.2%

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